# REMARKS

Status of the Claims

Claims 15-19 are pending. Claims 15-19 are rejected. Claims 16-18 are amended herein. Claims 15 and 19 are canceled.

Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Amendments to the claims

Dependent claims 16-18 are amended to overcome prior art rejections under 35 U.S.C. §103(a) as listed *infra*. No new matter has been added.

The 35 USC §103 Rejections

Claims 15 and 19 stand rejected under 35 USC §103(a) as unpatentable over **Bacus** *et al.* (USP 5,514,554, effective filing date 9/27/91) in view of **Rosenblum** *et al.* (*Cancer Communications*,

1991) and **Hudziak** *et al.* (*Molecular and Cellular Biology*, 1989). Claims 15 and 19 are cancelled.

Claims 15-19 *stand rejected under 35 USC §103(a) as unpatentable over* ***Wels*** *et* al. (USP 5,571,894, effective filing date 7/15/91) in view of **Hoogenboom** *et al.* (*Biochimica et Biophysica Acta*, 1991, Vol. 4, pp. 345-354) and **Hudziak** *et al.* (*Molecular and Cellular Biology*, 1989). Claims 15 and 19 are cancelled. The Applicant respectfully traverses the rejection of Claims 16-18.

**Wels** teaches an anti-erbB2 single chain antibody fused to a plant or bacterial toxin, and that such a fusion can retain the binding activity of the antibody as well as the activity of the toxin. **Hoogenboom** teaches a fusion protein between an antitransferrin single chain antibody and TNF as an immunotoxin against myeloma cells, with retention of antibody binding and TNF activity. **Hudziak** teaches the unconjugated administration of TNF and anti-erB2 antibodies in the treatment of breast cancer cells. The Examiner maintains that one of skill in the art would be motivated to make an immunotoxin to target breast cancer cells by fusing an anti-erbB2 antibody to TNF from the teachings of **Wels** and **Hudziak**, and would have a reasonable expectation of success from the teachings of

**Hoogenboom** of retention of antibody binding and TNF activity. Applicant respectfully disagrees.

Claims 16-18 are amended to be drawn specifically to a fusion protein of tumor necrosis factor to a single chain antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein; Claim 18 adds the limitation that the single-chain antibody is scFv23. The Applicant respectfully maintains that given the structural specificity and precision in the process of protein folding that defines each protein's activity, one skilled in the art would not be motivated to combine the teachings of **Wels** and **Hudziak** to arrive at the claimed fusion protein.

The biological activity of a protein depends on its folding into a highly organized three-dimensional structure under physiological conditions (The Encylcopedia of Molecular Biology, Sir John Kendrew Ed., Blackwell Science Ltd, London, 1994, p. 884). In **Hudziak**, the separate administration of unconjugated monoclonal anti-erbB2 antibody and TNF sensitizes breast cancer cells to TNF. The instant invention improves on **Hudziak** by administering TNF concurrently with the sensitizing antibody. However, one skilled in the art could not determine from the combination of **Wels** and

**Hudziak** whether a fusion protein between TNF and a single-chain anti-erbB2 antibody would retain antibody binding and TNF toxicity properties. It is likely that the fusion would disrupt the specific processes of protein folding in the separate entities, so that the binding regions essential to their function would be disrupted.

**Friedman** ***et al.*** (*Cancer Reseach,* Vol. 53, 1993, pp. 334-339) report that investigators have experienced a reduction in binding efficiency of 3- to 10- fold in recombinant antibody proteins compared to the corresponding non-recombinant IgG antibodies. In **Freidman**, a fusion protein formed between a single-chain sFv antibody and a *Pseudomonas* exotoxin fragment resulted in the production of a mixture of monomeric and aggregate proteins. The monomer was 5-fold less effective than the native IgG in binding to the target antigen, whereas the aggregate form was unable to bind. The aggregates mainly resulted from monomers that were misfolded during production, forming inappropriate disulfide bonds, hindering correct display of antigen-combining sites. Further experiments were therefore initiated to increase the antigen-binding activity of the recombinant immunotoxin molecule.

In **Chaudhary** ***et al.*** (*Nature,* Vol. 339, 1989, pp. 394-397), a fusion protein between a single-chain Fv antibody and a modified form of *Pseudomonas* exotoxin displayed a three-fold decrease in binding to the target antigen over the un-fused antibody.

It is therefore likely that time-consuming, non-routine experimentation, beyond that which is obvious to one skilled in the art, would be required to determine if the anti-erbB2-TNF fusion protein would exhibit the same effect as the separate administration of each component. One skilled in the art would also therefore not expect success in retaining the antibody binding and toxin activites in the fusion protein, as taught in **Hoogenboom**.

Therefore, the Applicants respectfully submit that claims 16-18 as not obvious under 35 USC §103(a) over **Wels** in view of and **Hudziak** and **Hoogenboom**. Accordingly, the Applicants respectfully request that the rejection of claims 16-18 under 35 USC §103(a) as obvious over **Wels** in view of and **Hudziak** and **Hoogenboom** be withdrawn.

This is intended to be a complete response to the final Office Action mailed May 23, 2002. If any issues remain

outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS:**

Please amend claim 16 as follows:

16. (amended) ~~The~~ A composition ~~of Claim 15,~~ comprising a fusion protein of tumor necrosis factor to a single chain antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. ~~wherein said conjugate is a fusion protein between said single chain antibody and tumor necrosis factor.~~

Please amend claim 17 as follows:

17. (amended) The composition of Claim ~~15~~ 16, wherein said ~~conjugate~~ fusion protein is recombinantly produced by fusing a gene encoding said single chain antibody to a gene encoding said tumor necrosis factor.

Please amend claim 18 as follows:

18. (amended) The composition of Claim ~~15~~ 16, wherein said single chain antibody is scFv-23.

Please cancel claims 15 and 19.